

Pacific University
CommonKnowledge

School of Physician Assistant Studies

Theses, Dissertations and Capstone Projects

Fall 8-9-2014

Efficacy of Opioid Antagonist in the Treatment of Pathological Gambling

Anne Hedges
Pacific University

Follow this and additional works at: <http://commons.pacificu.edu/pa>



Part of the [Medicine and Health Sciences Commons](#)

Recommended Citation

Hedges, Anne, "Efficacy of Opioid Antagonist in the Treatment of Pathological Gambling" (2014). *School of Physician Assistant Studies*. Paper 490.

This Capstone Project is brought to you for free and open access by the Theses, Dissertations and Capstone Projects at CommonKnowledge. It has been accepted for inclusion in School of Physician Assistant Studies by an authorized administrator of CommonKnowledge. For more information, please contact CommonKnowledge@pacificu.edu.

Efficacy of Opioid Antagonist in the Treatment of Pathological Gambling

Abstract

Background: Gambling is a legal form of entertainment in 48 states and is enjoyed by many. In Approximately 1% of the population, casual gaming can turn into pathological gambling (PG) resulting in devastating consequences. There are currently no guidelines or regulations for clinical providers regarding the most effective treatments of PG. Previous research has shown opioid antagonist to be effective in treating similar addictions such as alcoholism and heroin. How effective are opioid antagonist in the treatment of pathological gambling?

Methods: An exhaustive search of Medline-OVID, CINAHL, PSYCHINFO, Evidence Based Medicine Reviews Multifile, and Web of science using keywords: gambling, drug therapy, and narcotic antagonist. Limitations included studies in the English language and on humans. Articles pertaining to the area of interest were evaluated using GRADE.

Results: Three studies met inclusion criteria which are discussed in this systematic review. A randomized double-blind, placebo-controlled trial with 112 participants showed statistically significant reduction in gambling behaviors and urges with 18 weeks of treatment with naltrexone. Another randomized double-blind, placebo-controlled trial with 233 participants failed to show significant decrease in gambling behaviors and urges with 18 weeks of treatment with nalmefene compared. Finally, a case study showed complete cessation of gambling behavior and urges with intramuscular monthly injections of naltrexone.

Conclusion: Opioid antagonist drug naltrexone may be an effective option for treating pathological gambling whereas a similar drug nalmefene seems to be ineffective. Due to the low quality of evidence, effective injectable naltrexone effective dosing is undetermined.

Degree Type

Capstone Project

Degree Name

Master of Science in Physician Assistant Studies

Keywords

gambling, drug therapy, narcotic antagonist

Subject Categories

Medicine and Health Sciences

Rights

Terms of use for work posted in CommonKnowledge.

Copyright and terms of use

If you have downloaded this document directly from the web or from CommonKnowledge, see the “Rights” section on the previous page for the terms of use.

If you have received this document through an interlibrary loan/document delivery service, the following terms of use apply:

Copyright in this work is held by the author(s). You may download or print any portion of this document for personal use only, or for any use that is allowed by fair use (Title 17, §107 U.S.C.). Except for personal or fair use, you or your borrowing library may not reproduce, remix, republish, post, transmit, or distribute this document, or any portion thereof, without the permission of the copyright owner. [Note: If this document is licensed under a Creative Commons license (see “Rights” on the previous page) which allows broader usage rights, your use is governed by the terms of that license.]

Inquiries regarding further use of these materials should be addressed to: CommonKnowledge Rights, Pacific University Library, 2043 College Way, Forest Grove, OR 97116, (503) 352-7209. Email inquiries may be directed to: copyright@pacificu.edu

NOTICE TO READERS

This work is not a peer-reviewed publication. The Master's Candidate author of this work has made every effort to provide accurate information and to rely on authoritative sources in the completion of this work. However, neither the author nor the faculty advisor(s) warrants the completeness, accuracy or usefulness of the information provided in this work. This work should not be considered authoritative or comprehensive in and of itself and the author and advisor(s) disclaim all responsibility for the results obtained from use of the information contained in this work. Knowledge and practice change constantly, and readers are advised to confirm the information found in this work with other more current and/or comprehensive sources.

The student author attests that this work is completely his/her original authorship and that no material in this work has been plagiarized, fabricated or incorrectly attributed.

Efficacy of Opioid Antagonist in the Treatment of Pathological Gambling

Betsy Hedges



A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 9th 2014

Faculty Advisor: Saje Davis-Risen

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS

Biography

Betsy Hedges is a native of Dublin, Ohio. She received her Bachelor of Science degree from Arizona State University in Psychology in 2007. Prior to PA school she managed a vision therapy practice with her husband an optometrist and volunteered with Liga International's free medical clinics in Sinaloa, Mexico. She is interested in pursuing international medical relief work.

Abstract

Background: Gambling is a legal form of entertainment in 48 states and is enjoyed by many. In Approximately 1% of the population, casual gaming can turn into pathological gambling (PG) resulting in devastating consequences. There are currently no guidelines or regulations for clinical providers regarding the most effective treatments of PG. Previous research has shown opioid antagonist to be effective in treating similar addictions such as alcoholism and heroin. How effective are opioid antagonist in the treatment of pathological gambling?

Methods: An exhaustive search of Medline-OVID, CINAHL, PSYCHINFO, Evidence Based Medicine Reviews Multifile, and Web of science using keywords: gambling, drug therapy, and narcotic antagonist. Limitations included studies in the English language and on humans. Articles pertaining to the area of interest were evaluated using GRADE.

Results: Three studies met inclusion criteria which are discussed in this systematic review. A randomized double-blind, placebo-controlled trial with 112 participants showed statistically significant reduction in gambling behaviors and urges with 18 weeks of treatment with naltrexone. Another randomized double-blind, placebo-controlled trial with 233 participants failed to show significant decrease in gambling behaviors and urges with 18 weeks of treatment with nalmefene compared. Finally, a case study showed complete cessation of gambling behavior and urges with intramuscular monthly injections of naltrexone.

Conclusion: Opioid antagonist drug naltrexone may be an effective option for treating pathological gambling whereas a similar drug nalmefene seems to be ineffective. Due to the low quality of evidence, effective injectable naltrexone effective dosing is undetermined.

Keywords: *gambling, drug therapy, narcotic antagonist.*

Acknowledgements

To *Jake Hedges*, Thank you for your love and support through this journey.

Table of Contents

Biography.....	2
Abstract	3
Acknowledgements.....	4
Table of Contents	5
List of Tables	6
List of Abbreviations	6
BACKGROUND	7
METHODS	7
RESULTS	7
DISCUSSION	12
CONCLUSION.....	14
References	15
Table I. Characteristics of Reviewed Studies	16
Table II. Summary of Findings.....	17

List of Tables

Table I: Characteristics of Reviewed Studies

Table II: Summary of Finding

List of Abbreviations

CBT.....	Cognitive Behavior Therapy
CGI-S.....	Clinically Global Impressions-Severity of Illness scale
G-SAS.....	Gambling Symptom Assessment Scale
HAM-A.....	The Hamilton Rating scale for Anxiety
HAM-D.....	Hamilton Rating Scale for Depression
PG.....	Pathological gambling
PG-YBOCS..	Pathological Gambling Adaptation of Yale-Brown Obsessive Compulsive Scale
SDS.....	Sheehan Disability Scale
SOGS.....	South Oaks Gambling Screen

Efficacy of Opioid Antagonist in the Treatment of Pathological Gambling.

BACKGROUND

Currently in the United States, 48 states have some form of legalized gambling with the exception of Utah and Hawaii. Furthermore, the increase of internet gaming and casinos could potentially lead to an increase in PG. This easy access to gaming has the potential to create problematic and pathological gambling which affects approximately 1% of the US population.¹ Pathological gambling (PG) is a disorder that affects an individual financially, socially, and psychologically. The DSM-5 defines PG as a “persistent and recurrent maladaptive gambling behavior that disrupts personal, family, or vocational pursuits.”²

There are currently no protocols or guidelines in place for first line therapy in the treatment of PG. Opioid antagonist drugs have been shown to be effective treatment in similar compulsive disorders such as alcoholism and heroin addiction.^{3,4} Naltrexone and nalmefene (not available in US) are two opioid antagonists that may be useful in treating PG. The need for clear definition of effective treatments for PG needs to be established for healthcare providers to successfully provide adequate care.

METHODS

An exhaustive literature search was conducted using Medline-OVID, CINAHL, PSYCHINFO, Evidence Based Medicine Reviews Multifile, and Web of science using keywords: gambling, drug therapy, and narcotic antagonist. The search was further limited to the English language, research conducted in the United States, and human studies. Articles

pertaining to the area of interest were evaluated using Grading of Recommendations, Assessment, Development and Evaluation (GRADE).⁵

RESULTS

The original search yielded 13 articles. After eliminating non-relevant articles, three were included for review. These articles included two randomized control trials,^{6,7} and one case study.⁸ See Table I and Table II.

Naltrexone vs Placebo

This randomized, double blind placebo controlled study⁶ evaluated the safety and efficacy of three oral doses of naltrexone for the treatment of PG. Participants were obtained through newspaper advertisements. Recruits consisted of both men and women ages 18 to 75 years with a primary diagnosis of PG according to DSM-IV-TR criteria. Inclusion criteria included; a score of 2 or higher on the Gambling Symptom Assessment Scale (G-SAS), a score of 5 or higher on the South Oaks Gambling Screen (SOGS), and had a gambling encounter within 14 days of initiation of participation.⁶

Exclusion criteria included gambling less than once a week, not meeting DSM-IV-TR criteria for PG, unstable medical condition including abnormal laboratory tests, EKG, or physical exam upon enrollment. Women who were pregnant, lactating or not providing adequate birth control methods were excluded. A need for medication with contraindications with naltrexone, history of bipolar disorder, dementia, schizophrenia, substance abuse or dependence, positive urine drug screen, cognitive behavioral therapy within the past 3 months, previous treatment of naltrexone, baseline score of 26 or higher on the 24-item Hamilton Rating Scale for Depression (HAM-D), suicidality, treatment with investigational medication or neuroleptics within past 3 months, treatment with fluoxetine within 4 weeks or

psychotropic drugs 2 weeks before study initiation would also exclude participation in the study.⁶

The length of the study was 18 weeks. Eighty three eligible participants began a 1-week placebo. At the start of the 2nd week, if G-SAS scores had reduced by 50%, participants were deemed placebo responders and eliminated. Computer generated randomization assigned the remaining 77 subjects to four groups: 50mg/day, 100mg/day, 150mg/day, or placebo. Due to known adverse side effects of naltrexone all subjects were started at 25mg/day or placebo for 2 days and titrated up to the assigned group dosage by the first day of week 3. Compliance was evaluated by measuring urine florescence to detect riboflavin which was inserted into each capsule.⁶

PG symptoms were assessed with the Pathological Gambling Adaptation of the Yale-Brown Obsessive Compulsive Scale (PG-YBOCS) and severity was assessed using the SOGS, G-SAS, and the Clinical Global Impressions-Severity of Illness scale (CGI-S). Anxiety, depression, and psychosocial functioning were also assessed using the HAM-A, HAM-D, and Sheehan Disability Scale (SDS). Participants were assessed weekly for two months and the remaining 10 weeks were assessed every two weeks.⁶

Twenty eight participants dropped out of the study. A lack of differences between the three naltrexone groups in regards to baseline characteristics, treatment completion, compliance, adverse drug reactions, and study outcomes led to the data of all groups being combined and compared to placebo. After 6 weeks of treatment 39.7% of those assigned to naltrexone had abstained completely from gambling for at least 1 month. After 6 weeks of those assigned to the placebo only 10.5% had abstained from gambling for at least 1 month. The PG-YBOCS, G-SAS, CGI-S, SDS all demonstrated improvement in scores in the

naltrexone groups. The Hamilton Rating scale for Anxiety (HAM-A) and HAM-D scores did not show an improvement in any study group. No changes to liver function or clinical findings occurred with the treatment of naltrexone. The study concluded that naltrexone was superior to placebo in the treatment of PG. Results also revealed that treatment outcomes were similar at 50mg, 100mg, and 150mg doses. Higher doses of naltrexone were not correlated with better outcomes.⁶

Limitations identified by the researches of this study included the length of the study being 18 weeks. PG has been identified as a chronic problem and longer treatment studies are needed. Also the study was limited to participants desiring a pharmacological intervention for PG excluding all psychotherapy treatment modalities. The authors identified that further research in the combination of naltrexone and cognitive behavior therapy are needed.⁶

Nalmefene vs Placebo

This randomized, double blind, placebo controlled study⁷ evaluated the safety and efficacy of two oral doses of nalmefene for the treatment of PG over 16 weeks. All research was funded by Somaxon pharmaceuticals. Participants were recruited via newspaper advertisement and consisted of both men and women ages ranging from 18-70. The research took place at 25 outpatient centers throughout the United States. Inclusion criteria included a score of 21 or higher on the PG-YBOCS , a score >5 on one criteria of the Sheehan Disability Scale (SDS) , and had a gambling even within one month of enrollment. Exclusion criteria consisted of a concurrent Axis I disorder, receiving treatment for gambling, and unstable medical illness.⁷

All participants began a one week placebo which was single-blinded. Participants who scored 15 or greater on the PG-YBOCS after the one-week placebo trial were randomized using a computer generated assignment to three groups: nalmefene 20mg/day, 40mg/day, or placebo. Due to known adverse drug reactions to opioid antagonist all randomized participants during week 2 began a 5mg/day dose of nalmefene or placebo equivalent. Doses were increased during week 3 according to assigned group. The PG-YBOCS total score was used to determine the primary outcome and G-SAS and SDS scores were used to measure secondary outcomes. Two hundred twenty-three randomized participants were prognostically balanced and used in analysis of the results.⁷

Seventy-seven participants were assigned to 20mg/day dose, 82 were in the 40mg/day dose, and 74 took the placebo. Placebo responders eliminated accounted for 46.8% in the 20mg/day, 56.1% in the 40mg/day, and 59.5% in the placebo group were eliminated after the first week. Analysis of the comparison of treatment response at either dose failed to show nalmefene was more effective than placebo ($F=1.741$, $d.f.=2$, $P=0.178$). However, post hoc analysis revealed that participants who had a fully titrated dose for a minimum of one week had improved PG-YBOCS scores, specifically a decrease in urges for gambling.⁷

The researchers identified that the poor results may have been due to the large number of treatment centers involved in the trial. Further investigation into the large portion of participant drop outs, 27% prior to the full titration dose in the treatment groups. Dropout rates may be due to adverse drug reactions of nalmefene or extraneous factors that should be accounted for in future research. A further limitation identified was the length of research. PG effective treatment may require longer than 18 weeks for improvement in urges and behavior.⁷

Injectable Naltrexone

This case study⁸ involved a 58 year old male with a history of alcohol dependence and depression in remission who became a PG after the initiation of taking pramipexole for restless leg syndrome. Although his restless leg symptoms ceased he began having urges to gamble and suffered losses of over \$100 000. The patient was titrated up to 200mg/day of oral naltrexone as prescribed by his clinician. Treatment of his restless leg was switched from pramipexole to clonazepam. After two weeks of treatment the patient reported no decrease in symptoms and gambling losses continued up to \$2 000 a month even post pramipexole cessation. The patient admitted to poor compliance with the oral naltrexone. An inpatient residential, 5-week intervention program was attempted but unsuccessful. A trial of 380mg/month injected intramuscularly naltrexone was initiated and within a month the patient reported no intent to gamble. Clonazepam was not effective in treating his restless leg symptoms and was started on pramipexole again. With the combination of pramipexole and injectable naltrexone the patient was able to abstain from all gambling for 12 months.⁸

DISCUSSION

Opioid antagonist drugs have an important role in the treatment of PG. Oral and injectable naltrexone was shown to be beneficial in decreasing gambling urges and total cessation of gambling behavior. Nalmefene was originally thought to be a better opioid antagonist pharmaceutical choice over naltrexone due to its longer half-life, stronger affinity for muscarinic opioid receptors, and no known associated liver toxicity. However, the randomized clinical trials,^{6,7} showed naltrexone to be superior to nalmefene. Nalmefene was shown to be equal to and in some cases less beneficial in treating overall PG recovery than the placebo.⁷

Although the naltrexone randomized clinical trial⁶ and the case study⁸ showed promising results for PG treatment there were limitations with these findings. The recruitment for the naltrexone RCT⁶ was done through newspaper advertisement. Although inclusion and exclusion criteria were followed to participate in the trial, this type of recruitment involves participants already with a desire to quit gambling. This may have led to elevated results in both the treatment group and the placebo.

Both RCTs^{6,7} had a considerable amount of subjects terminate participation prematurely. The naltrexone study⁶ had a 36% dropout and the nalmefene study⁷ had a 27%. It is unclear in both studies for the reason of attrition rates. Further investigation of whether adverse drug or lack of interest in continuing treatment lead to the discontinuation of participation.

The case study⁸ is severely limited due to a sample size of 1. The results cannot be generalized to the PG community until a larger study is performed using injectable naltrexone for decreasing gambling urges and behaviors.

Limitations to the Nalmefene RCT⁷ were similar to the naltrexone RCT⁶ in that they used the same form of recruitment. This may have led to the results showing the placebo being more effective than nalmefene due to the participants desire to seek help and cease gambling behavior from the start of the trial. Future studies should involve participants should include persons with a PG diagnosis with the desire to stop gambling and those with no desire to stop to measure to true effectiveness of treatment.

CONCLUSION

Due to the lack of recommended first line treatments or protocols by American medical associations for treatments of PG, opioid antagonist naltrexone is a viable option for clinicians. A 50mg/day oral dose of naltrexone may be appropriate for treatment of adults with PG. If non-compliance leads to treatment failure, injectable naltrexone is a consideration if no other options are available. Future research is necessary in order to fully understand opioid antagonist use in the treatment of PG.

References

1. Shaffer HJ, Hall MN, Vander Bilt J. Estimating the prevalence of disorder gambling behavior in the United States and Canada: a research synthesis. *Am J Public Health*. 1999;89:1369-1376.
2. American Psychiatric Association ApaDSMTF. Diagnostic and statistical manual of mental disorders: DSM-5. American Psychiatric Association, Arlington, VA (2013).
3. Martin WR, Jasinski D, Mansky P. Naltrexone, an antagonist for the treatment of heroin dependence. *Arch Gen Psychiatry* 1973; 23: 784– 789.
4. Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP. Naltrexone in the treatment of alcohol dependence. *Arch Gen Psychiatry* 1992; 49: 876– 880.
5. GRADE working group. GRADE website. <http://gradeworkinggroup.org/>. Accessed Oct 1, 2013.
6. Grant JE, Kim SW, Hartman BK. A double-blind, placebo-controlled study of the opiate antagonist naltrexone in the treatment of pathological gambling urges. *J. Clin. Psychiatry* 69(5), 783-789 (2008).
7. Grant JE, Odlaug BL, Potenza MN, Hollander E, Kim SW. Nalmefene in the treatment of pathological gambling; multicentre, double-blind, placebo-controlled study. *Br. J. Psychiatry* 197(4), 330-331 (2101).
8. Yoon G, Kim SW. Monthly injectable naltrexone for pathological gambling. *Am J Psychiatry* 2013; 170(6):682-683.

Table I. Characteristics of Reviewed Studies

Quality Assessment							
Study Detail		Downgrade Criteria					
Participants	Design	Limitations	Indirectness	Imprecision	Inconsistency	Publication bias likely	Quality
A Double-Blind, Placebo-controlled Study of the Opiate Antagonist Naltrexone in the Treatment of Pathological Gambling Urges.⁶							
112	RCT	No serious limitations	No serious indirectness	No serious imprecision	No serious inconsistencies	No	High
Nalmefene in the Treatment of Pathological Gambling: multicenter, double-blind, placebo-controlled study.⁷							
233	RCT	Serious limitations ^a	No serious indirectness	Serious imprecision ^b	No serious inconsistencies	No ^c	Low
Monthly Injectable Naltrexone for Pathological Gambling.⁸							
1	Case Study	Serious limitations ^d	-	-	-	-	Very Low

^a as evidenced by subgroup analysis participants were not on the study long enough

^bHigh attrition rate

^cFunded by Somaxon pharmaceutical but study failed to show significant results

^dSmall sample size

Table II. Summary of Findings

Summary of Findings							Importance
	Number of Patients		Effect				
Study	Opioid Antagonist	Placebo	Baseline	End Point	Effect size	p-value/ CI	
PG-YBOCS total score							
Naltrexone vs placebo	36	13	Placebo18.6±4.90 Naltrexone 16.9± 6.60	Placebo12.9± 9.31 Naltrexone 9.7±8.12	3.05	.009	Critical
Nalmefene vs placebo	20mg n=59 40mg n = 57	n= 71	Placebo 21.98 Nalmefene 20mg 21.17 Nalmefene 40mg 20.75	Placebo 11.29-12.26 Nalmefene 20mg 11.34-12.30 Nalmefene 40mg 6.06-7.21	20mg = 0.49 40mg = -1.96	95%	Critical
IM Naltrexone	1	0	-	-	-	-	
PG-YBOCS urge scale							
Naltrexone vs placebo	36	13	Placebo10.2±2.66 Naltrexone 9.5±3.54	Placebo7.1± 4.73 Naltrexone 5.5±4.16	1.66	.005	Critical
Nalmefene vs placebo	20mg n=59 40mg n = 57	n= 71	Placebo 11.33 Nalmefene 20mg 10.83 Nalmefene 40mg 11.09	Placebo 6.01-6.48 Nalmefene 20mg 5.74-6.22 Nalmefene 40mg 4.04-4.61	20mg = 0.49 40mg = -1.96	95%	Critical
IM Naltrexone	1	0	-	-	-	-	